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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
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☐ *Additional inventors are being named on the _____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Pharmaceutical Compositions for Enhanced Topical Application

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification *Number of Pages* 28
☒ Drawing(s) *Number of Sheets* 16
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fees
☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 03-3975
☐ Payment by credit card. Form PTO-2038 is attached.

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

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Date Jul 11, 2003

REGISTRATION NO. *(if appropriate)* 26,588

Docket Number: 044050-0303481

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S.D Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

PHARMACEUTICAL COMPOSITIONS FOR ENHANCED TOPICAL APPLICATION

FIELD OF USE

[0001] The present invention relates generally to a pharmaceutical composition for administration of active agents through the skin and other membranes and methods of using the same.

BACKGROUND OF THE INVENTION

[0002] Recently, transdermal therapeutic formulations have been developed to deliver active agents to the body via the skin or other membranes, e.g., mucosa. These formulations offer the advantages of allowing the active agents to evade metabolism in the intestine and liver, reduce side reactions and provide a longer pharmacological effect. However, their use has been limited because skin naturally provides a barrier to foreign substances, such as most active agents. Therefore, only limited kinds of active agents can attain effective concentrations in skin tissues and within the bloodstream.

[0003] Various attempts have been made to overcome these problems. One approach has been to increase percutaneous absorption of active agents by decreasing the barrier property of skin through the use of skin penetration enhancing (SPE) compounds. However, problems with compatibility of SPE compounds with the active agents and/or carriers or generally with efficacy of the enhancers continues to occur. In addition, skin irritation and other systemic and local side effects have proven to be problematic. Further improvements are still needed to overcome these problems.

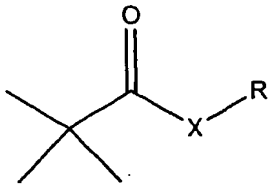
SUMMARY OF THE INVENTION

[0004] The present invention provides pharmaceutical compositions for the transdermal administration of an active agent to a mammal, such as a human, by applying the composition to an area of skin in the presence of a new class of SPE compounds.

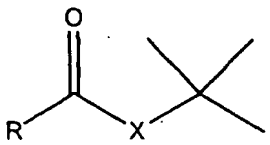
[0005] Thus, one embodiment of the invention provides a pharmaceutical composition for transdermal administration comprising an active agent and a skin penetration enhancer.

[0006] Another embodiment of the present invention provides a pharmaceutical composition for transdermal administration comprising:

1) a skin penetration enhancer represented by Formula IA and/or IB as shown below:



IA



IB ;

2) an active agent; and

3) a vehicle.

[0007] In another embodiment, the present invention provides methods for administering an active agent by use of the pharmaceutical compositions described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Figure 1 is a graph showing the measured flux of Ibuprofen as a function of time across human skin when applied as a 5% solution of Ibuprofen in ethanol alone (15), or as an ethanolic solution containing 10% N-decyl pivalamide (38), or 10% N-dodecyl pivalamide (39). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0009] Figure 2 is a graph showing cumulative transfer of Ibuprofen across human skin as a function of time when applied as a 5% solution of Ibuprofen in ethanol alone (15), or as an ethanolic solution containing 10% N-decyl pivalamide (38), or 10% N-dodecyl pivalamide (39). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0010] Figure 3 is a graph showing the measured flux of Ibuprofen as a function of time across human skin when applied as a 5% solution of Ibuprofen in ethanol alone (15), or as an ethanolic solution containing 10% lauryl pivalate (14). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0011] Figure 4 is a graph showing cumulative transfer of Ibuprofen across human skin as a function of time when applied as a 5% solution of Ibuprofen in ethanol alone (15), or as an ethanolic solution containing 10% lauryl pivalate (14). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0012] Figure 5 is a graph showing the measured flux of Ibuprofen as a function of time across human skin when applied as a 5% solution of Ibuprofen in ethanol alone (15), or as an ethanolic solution containing 10% t-butyl decanoate (25). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0013] Figure 6 is a graph showing cumulative transfer of Ibuprofen across human skin as a function of time when applied as a 5% solution of Ibuprofen in ethanol alone (15), or as an ethanolic solution containing 10% t-butyl decanoate (25). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0014] Figure 7 is a graph showing the measured flux of PGE-1 as a function of time across human skin when applied as a 2% solution of PGE-1 in ethanol alone, or as an ethanolic solution containing 10% t-butyl decanoate (28), 10% t-butyl myristate (29), 10% t-butyl laurate (30), 10% lauryl pivalate (32), or 10% tetradecyl pivalate (51). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0015] Figure 8 is a graph showing cumulative transfer of PGE-1 across human skin as a function of time when applied as a 2% solution of PGE-1 in ethanol alone, or as an ethanolic solution containing 10% t-butyl decanoate (28), 10% t-butyl myristate (29), 10% t-butyl laurate (30), 10% lauryl pivalate (32), or 10% tetradecyl pivalate (51). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0016] Figure 9 is a graph showing the measured flux of PGE-1 as a function of time across human skin when applied as a 2% solution of PGE-1 in ethanol alone, or as an ethanolic solution containing 10% N-decyl pivalamide (52), or 10% N-dodecyl pivalamide (53). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0017] Figure 10 is a graph showing cumulative transfer of PGE-1 across human skin as a function of time when applied as a 2% solution of PGE-1 in ethanol alone, or as an ethanolic solution containing 10% N-decyl pivalamide (52), or 10% N-dodecyl pivalamide (53). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0018] Figure 11 is a graph showing the measured flux of testosterone as a function of time across human skin when applied as a 1% solution of testosterone in ethanol alone (7), or as an ethanolic solution containing 10% lauryl pivalate (6). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0019] Figure 12 is a graph showing cumulative transfer of testosterone across human skin as a function of time when applied as a 1% solution of testosterone in ethanol

alone (7), or as an ethanolic solution containing 10% lauryl pivalate (6). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0020] Figure 13 is a graph showing the measured flux of testosterone as a function of time across human skin when applied as a 1% solution of testosterone in ethanol alone (7), or as an ethanolic solution containing 10% t-butyl myristate (27), 10% N-decyl pivalamide (42), or as a 10% N-dodecyl pivalamide (43). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0021] Figure 14 is a graph showing cumulative transfer of testosterone across human skin as a function of time when applied as a 1% solution of testosterone in ethanol alone (7), or as an ethanolic solution containing 10% t-butyl myristate (27), 10% N-decyl pivalamide (42), or as a 10% N-dodecyl pivalamide (43). Parenthetical numbers are in reference to the solutions reported in Table 1.

[0022] Figure 15 is a graph showing the measured flux of testosterone as a function of time across human skin when applied as a 1% solution of testosterone in ethanol alone (7), or as an ethanolic solution containing 10% t-butyl decanoate. Parenthetical numbers are in reference to the solutions reported in Table 1.

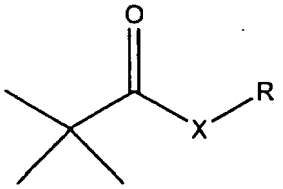
[0023] Figure 16 is a graph showing cumulative transfer of testosterone across human skin as a function of time when applied as a 1% solution of testosterone in ethanol alone (7), or as an ethanolic solution containing 10% t-butyl decanoate. Parenthetical numbers are in reference to the solutions reported in Table 1.

DETAILED DESCRIPTION

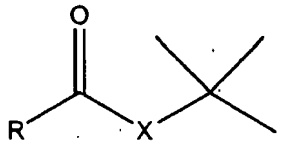
[0024] As used herein the following terms have the following meanings: "pharmaceutically acceptable" refers to substances that, when taking into account the benefits versus the risks, are acceptable for use with mammals, including humans, without undue adverse side effects (such as toxicity, irritation, and allergic response).

Skin Penetration Enhancers

[0025] The skin penetration enhancer compounds of the present invention, are selected from compounds represented by Formulas IA or IB:



IA



IB

wherein: R represents a linear, saturated or unsaturated, substituted or unsubstituted hydrocarbyl radical; and X is either an oxygen atom or an NH radical.

[0026] A preferred class of compounds of Formulas IA and IB is where R represents a linear C_6-C_{20} alkyl radical, for example, a C_6-C_{16} alkyl radical, a C_{6-14} alkyl, or a C_8-C_{14} alkyl radical. Preferably, R represents a C_8-C_{14} linear alkyl radical, for example, an octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, or tetradecyl radical, for example an octyl, decyl, dodecyl or tetradecyl radical.

[0027] Exemplary skin penetration enhancer compounds of Formulas IA and IB include decyl pivalate, dodecyl pivalate, tetradecyl pivalate, N-decyl pivalamide, N-dodecyl pivalamide, tert-butyl decanoate, tert-butyl laurate, and tert-butyl myristate.

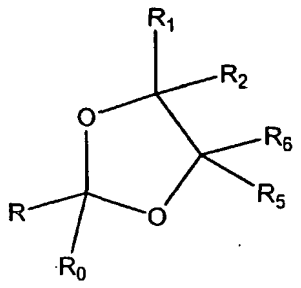
[0028] Often, amide compounds of Formulas IA or IB generally provide less odor and may be more stable in formulations containing them.

[0029] The enhancers of the present invention may be present from about 1 or 2% to about 15 or 20 % of the weight of this composition, for example, from about 2 to about 10%, for example 5%.

[0030] Compounds according to Formulas IA and IB may be synthesized by techniques known in the art. For example, esters of these Formulas can be synthesized by an esterification reaction between the constituent alcohol and acid. See, for example, Wiener and Gilon, J. Mol. Catalysis 37: 45-52, 1986.

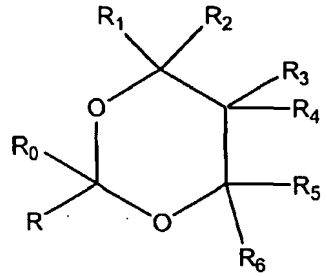
[0031] The skin penetration enhancing compounds of Formulas IA or IB may be used individually or in combination with each other or in admixture with other known skin penetration enhancing compounds, such as those described below.

[0032] Known skin penetration enhancing compounds which may be used in combination with the compound(s) of Formula IA and/or IB include, for example: 2-substituted 1,3-dioxolanes of the formula (I):



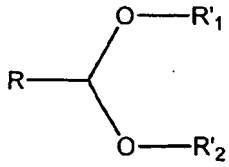
(I)

or a 1,3-dioxane of the formula (II):



(II)

or an acetal (including hemiacetal) of the formula (III):



(III)

where R represents a C_6 to C_{20} aliphatic group, R_1, R_2, R_3, R_4, R_5, and R_6, each, independently, represent hydrogen or a C_1 to C_4 aliphatic group; R'_1 and R'_2, each, independently, represent C_1 to C_4 aliphatic group. Several compounds of these formulas are available commercially from MacroChem Corporation under the trademark SEPA®.

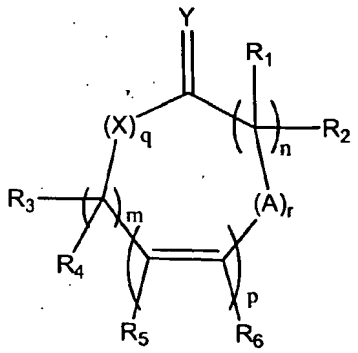
[0033] R may also represent a C_6 to C_{12} aliphatic group; especially C_7 to C_{10} aliphatic group. The aliphatic group may be a straight or branched chain alkyl or alkenyl group, such as, for example, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-hexadecyl, n-octadecyl, 2-methyl-octyl, 4-ethyl-decyl, 8-methyl-decyl, n-octenyl, n-stearyl, and the like.

[0034] The C_1 to C_4 aliphatic group may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, ethenyl, and the like. For example, R_1 to R_6 may represent aliphatic groups and R'_1 and R'_2 may represent alkyl groups, for example, alkyls having 1 or 2 carbon atoms, such as ethyl. R_1 to R_6 may also all be hydrogen.

[0035] Representative skin penetration enhancing compounds (i) include, for example, 2-n-heptyl-1,3-dioxolane, 2-n-nonyl-1,3-dioxolane, 2-n-undecyl-1,3-dioxolane, 2-n-nonyl-1,3-dioxane, 2-n-undecyl-1,3-dioxane, 2-n-heptylaldehyde-acetal, 2-n-octyl-aldehyde-acetal, 2-n-nonylaldehyde-acetal, 2-n-decylaldehyde-acetal, 3,7-dimethyl-2,6-octadienal (citral), citronal and the like.

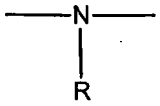
[0036] Another class of skin penetration enhancing compounds (ii) are cyclic ketones and cyclic lactones and derivatives thereof, as disclosed in, for example, U.S. Patent Nos. 5,023,252 and 5,731,303, the disclosures of which, are incorporated herein, in their entireties, by reference thereto.

[0037] The skin penetration enhancing compounds (ii) may be represented by the following formula (IV):

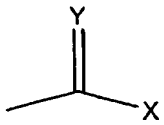


(IV)

wherein X and Y are oxygen, sulfur or an imino group of the structure



or =N-R, with the proviso that when Y is the imino group, X is an imino group, and when Y is sulfur, X is sulfur or an imino group, A is group having the structure



wherein X and Y are defined above,

m and n are integers having a value from 1 to 20 and the sum of m+n is not greater than 25,

p is an integer having a value of 0 or 1,

q is an integer having a value of 0 or 1,

r is an integer having a value of 0 or 1,

R represents hydrogen or a straight or branched chain alkyl group having from 1 to 6 carbon atoms, and,

R_1, R_2, R_3, R_4, R_5 and R_6, each, independently, represent hydrogen or a straight or branched chain alkyl group having from 1 to 6 carbon atoms, with the proviso that only one of R_1 to R_6 may be said alkyl group, and with the further provisos that,

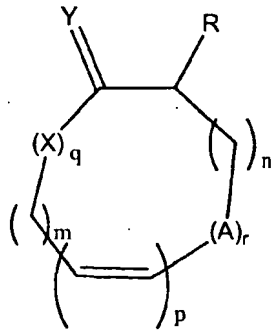
when p, q and r have a value of 0 and Y is oxygen, m+n is at least 11,

when X is an imino group, q equals 1, Y is oxygen, and p and r are 0, then m+n is at least 11.

[0038] Examples of the alkyl group for R and R_1 to R_6 include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, amyl, hexyl, and the like.

[0039] For example, each of R and R_1 to R_6 may represent hydrogen atoms and X and Y may each represent oxygen. Compounds represented by formula (IV) may be cyclic ketones (when q and r are each 0) or cyclic lactones.

[0040] Other compounds of formula (IV) may be represented by the following general formula (IV-A):



(IV-A)

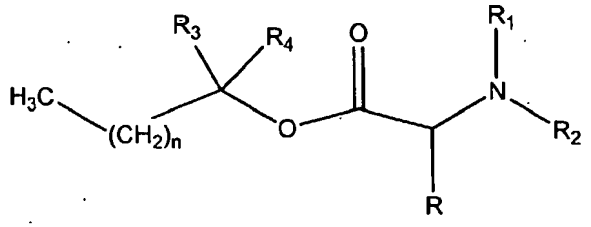
wherein X, Y, R, A, m, n, p, q and r, are as defined above.

[0041] For example, in formula (IV-A), X and Y are each oxygen and R represents hydrogen.

[0042] For example, pentadecalactone is a skin penetration enhancer of type (ii).

[0043] Another class of skin penetration enhancing compounds (iii) include an alkyl-2-(N,N-disubstitutedamino)-alkanoate, an (N,N-disubstituted amino)-alkanol alkanoate, or a mixture of these, as more fully described in U.S. 6,046,244, the disclosure of which is incorporated herein by reference thereto. For convenient reference, alkyl-2-(N,N-disubstituted amino)-alkanoates and (N,N-disubstituted amino)-alkanol alkanoates can be grouped together under the label alkyl (N,N-disubstituted amino) esters.

[0044] Alkyl-2-(N,N-disubstituted amino)-alkanoates useful as skin penetration enhancers may also be represented by the following formula (V)



(V)

wherein n is an integer having a value in the range of about 4 to about 18;

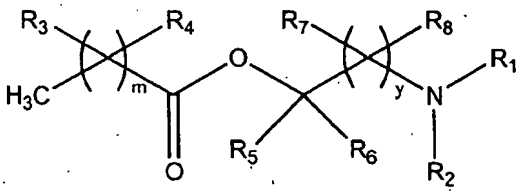
R is a member of the group consisting of hydrogen, C_1 to C_7 alkyl, benzyl and phenyl;

R_1 and R_2 are members of the group consisting of hydrogen and C_1 to C_7 alkyl; and R_3 and R_4 are members of the group consisting of hydrogen, methyl and ethyl.

[0045] Preferred alkyl (N,N-disubstituted amino)-alkanoates are C_4 to C_{18} alkyl (N,N-disubstituted amino)-acetates and C_4 to C_{18} alkyl (N,N-disubstituted amino)-propionates. Exemplary specific alkyl-2-(N,N-disubstituted amino)-alkanoates include dodecyl 2-(N,N dimethylamino)-propionate (DDAIP); and dodecyl 2-(N,N-dimethylamino)-acetate (DDAA).

[0046] Alkyl-2-(N,N-disubstituted amino)-alkanoates are known. For example, dodecyl 2-(N,N-dimethylamino)-propionate (DDAIP) is available from Steroids, Ltd. (Chicago, Ill.). In addition, alkyl-2-(N,N-disubstituted amino)-alkanoates can be synthesized from more readily available compounds as described in U.S. Pat. No. 4,980,378 to Wong et al., which syntheses procedures are incorporated herein by reference.

[0047] Suitable (N,N-disubstituted amino)-alkanol alkanoates can be represented by the formula (VI):

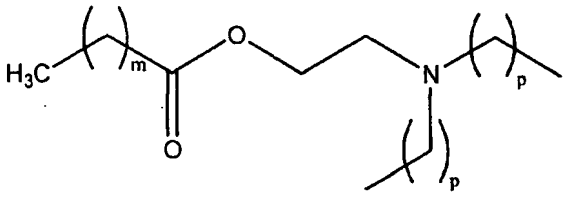


(VI)

wherein m is an integer having a value in the range of about 5 to about 22, preferably, from about 5 to about 18; y is an integer having a value in the range of 0 to

about 5; and R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are members of the group consisting of hydrogen, C_1 to C_8 alkyl, and C_6 to C_8 aryl; and R_8 represents hydrogen, hydroxyl, C_1 to C_8 alkyl, or C_6 to C_8 aryl.

[0048] (N,N-disubstituted amino)alkanol alkanoates include C_5 to C_{18} carboxylic acid esters, such as the compounds of the following formula (VI-1):



(VI-1)

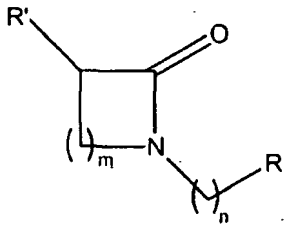
where m' is an integer of from about 5 to about 21, preferably, from about 5 to about 16; and p is an integer of from 0 to about 3, preferably, 0 or 1, especially 0.

[0049] Exemplary specific alkyl alkanoate compounds of formula (VI) include 1-(N,N-dimethylamino)-2-propanol dodecanoate (DAIPD), 1-(N,N-dimethylamino)-2-propanol myristate (DAIPM), and 1-(N,N-dimethylamino)-2-prpoanol oleate (DAIPO).

[0050] Other skin penetration enhancers include DDAIP and DAIPD may be specifically mentioned.

[0051] Another class of penetration enhancers of type (iv) include N-alkyl lactams, such as those disclosed in, for example, U.S. Patent Nos. 4,316,893 and 4,424,210, the disclosures of which are incorporated herein, in their entirety, by reference thereto; and N-alkylazacycloheptanes, such as those disclosed in, for example, U.S. 5,204,339, the disclosure of which is incorporated herein, in its entirety, by reference thereto.

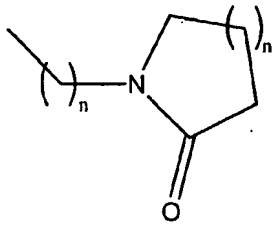
[0052] The N-alkyl lactams include, for example, compounds of the following formula (VII):



(VII)

m is an integer of 3 to 7, n is 0 or an integer of 1 to 17, except that when m is 3, n is from 7 to 17, and R is preferably methyl.

[0053] A class of lactams represented by the following formula (VII-1) may also be used as SPE's:



(VII-1)

where n = 0 or 1, and n" = 0, 1 or 2.

[0054] Examples of compounds of formula (VII) include:

1-n-hexylazacyclopentan-2-one

1-n-heptaylazacyclopentan-2-one

1-n-octylazacyclopentan-2-one

1-n-nonylazacyclopentan-2-one

1-decylazacyclopentan-2-one

1-n-dodecylazacyclopentan-2-one

1-methylazacycloheptan-2-one

1-n-propylazacycloheptan-2-one

1-n-butylazacycloheptan-2-one

1-n-octylazacycloheptan-2-one

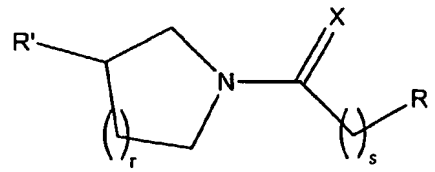
1-phenylazacyclopentan-2-one

1-(2-chlorophenyl)azacyclopentan-2-one

1,3-bis-(1-azacyclopentan-2-onyl)propane.

[0055] Of these, 1-n-dodecyl-azacycloheptan-2-one, is commercially available under the tradename, AZONE.

[0056] The N-alkylazacycloheptanes may be represented by the following formula (VIII):



(VIII)

where X represents O or S, preferably O, R' represents H or C_1 to C_4 alkyl; r is an integer of from 2 to 6, and s is 0 or an integer of 1 to 17.

[0057] Representative compounds of formula (VIII) include:

1-n-undecylformylazacycloheptane

1-n-decylformylazacycloheptane

1-n-octylformylazacycloheptane

1-n-nonylformylazacycloheptane

1-n-dodecylformylazacycloheptane

1-n-tetradecylformylazacycloheptane

1-n-hexadecylformylazacycloheptane

1-n-pentadecylformylazacycloheptane

1-n-heptadecylformylazacycloheptane

1-(16-methylhexadecyl)formylazacycloheptane.

[0058] Furthermore, unless the context indicates otherwise, terms such as "transdermal" or "skin" should be construed to also include penetration through the outer layer of various plant forms, such as trees, flowering plants, cacti, and like, including, for example, stems, leaves, shoots and the like.

Active Agents

[0059] An "active agent" refers either to a substance intended, after administration, to bring about a preventive, therapeutic, or beneficial response or condition in a subject, or to a combination of two or more substances of this type. Accordingly, the term "active agent" is intended to refer to that ingredient or ingredients in the composition which is intended to and expected to have a half-life of more than a few minutes (e.g., at least 2, preferably at least about 5 minutes) after introduction into the body, and are the ingredient(s) included to accomplish, in the case of a drug or other medicinal or pharmacological agent, a therapeutic, pharmaceutical, or cosmetic effect, or in the case or an agricultural agent, an equivalent therapeutic outcome, agriculturally.

[0060] The desired active agents may be provided in the form of a salt, solvate or prodrug thereof. The active agents of the present invention may also include the racemic mixtures or individual enantiomers of the above agents where applicable. The present invention may comprise active agents which are: polar, non-polar, hydrophilic, lipophilic, water soluble or water insoluble.

[0061] Various active agents which may be incorporated into compositions according to the invention, include, for example:

[0062] a bronchodilator such as sodium cromoglycate salbutamol or theophylline;

[0063] a diuretic agent such as furosemide or hydrochlorothiazide;

[0064] an antibacterial agent such as a penicillin, a cephalosporine, tetracycline, oxytetracycline, chlortetracycline or chloramphenicol;

[0065] an antifungal agent such as amorolfine, isoconazole, clotrimazole, econazole, miconazole, nystatin, terbinafine, bifonazole, amphotericin, griseofulvin, ketoconazole, fluconazole and flucytosine, salicylic acid, fezatione, ticlatone, tolnaftate, triacetin, zinc pyrithione;

[0066] an antiacne agent such as erythromycin;

[0067] a sedative or tranquillizer such as pentobarbital, secobarbital or codeine;

[0068] a psychostimulant such as 3-(2-aminopropyl)indole acetate or 3-(2-aminobutyl)indole acetate;

[0069] an anxiolytic agent such as diazepam, chlordiazepoxide, reserpine, chlorpromazine, buspirone hydrochloride or thiopropazate;

[0070] an oestrogen such as oestradiol, oestriol, oestrone, ethinyloestradiol, mestranol, stilboestrol, dienoestrol, epioestriol, estropipate and zeranol;

[0071] a hormonal drug (hormone) such as, for example Androgens, such as, for example, androstenediol and androisoxazole, testosterone, dihydrotestosterone, dehydroepiandrostenone; estrogens, such as, for example, 17 beta-estradiol, estradiol-3,17-diacetate, estradiol-3-acetate, estradiol-17-acetate, estradiol-3,17-valerate, estradiol-3-valerate, estradiol-17-valerate, ethinyl estradiol, estrone; progesterones, such as, for example, progesterone (preg-4-ene-3,20-dione), norethindrone, norgestrieone, norgestadienone, norgestrel, norgestimate, progestogenic acid, dihydroprogesterol, nomagesterol. Furthermore, in the above listed exemplary hormones, the testosterone

hormone may be used in any of its usual forms, such as, for example, acetate, propionate, 17-beta-cyclopentane-propionate, enanthanate, isobutyrate, undeconate, and the like.

[0072] Similarly, the estradiols may additionally be used in any of the known or newly developed forms, such as, for example, pivalate, propionate, cypionate, benzoate and other esters. Among these, especially preferred, based on the current level of knowledge in the pharmacological arts, are testosterone, progesterone and estradiol, in any of the salt or ester forms. More generally, however, any of the government approved hormones, such as listed in, for example, the most current edition of The Merck Index, may be advantageously used:

[0073] an ovulation inducer such as clomiphene;

[0074] an antipyretic agent such as acetylsalicylic acid, salicylamide, sodium salicylate or methyl salicylate;

[0075] a narcotic analgesic such as morphine or a major analgesic;

[0076] a hypoglycaemiant, for example a sulphonylurea such as glypizide, glyburic, chlorpropamide or insulin;

[0077] an antispasmodic agent such as atropine or methscopolamine bromide;

[0078] an antimalaria agent such as 4-aminoquinoline or 9-aminoquinoline;

[0079] a beta-blocker such as metoprolol;

[0080] an antiarthritic agent such as sulindac;

[0081] a non-steroidal antiinflammatory drug (NSAID), such as heteroaryl acetic acids, such as, for example, tolmetin, diclofenac, ketorolac; arylpropionic acids, such as, for example, ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin; anthranilic acids (fenamates), such as, for example, mefenamic acid, meclofenamic acid, fhilenamic acid; enolic acids, such as, for example, oxicams (e.g., piroxicam, tenoxicam),

pyrazolidinediones (e.g., phenylbutazone, oxyphenthatrazone); alkanoes, such as, for example, nabumetone. Among these, especially preferred, based on the current level of knowledge in the pharmacological arts, are ibuprofen, diclofenac, ketorolac, naproxen, flurbiprofen, ketoprofen and piroxicam.

[0082] More generally, however, any of the government approved NSAIDs, such as listed in, for example, the most current edition of The Merck Index, may be advantageously used:

[0083] an anti-osteoporotic agent such as etidronate, or tiludronate;

[0084] a skin bleaching agent or a skin decolorant or depigmentor, such as ascorbic acid or hydroquinone;

[0085] a vasodilator such as dipyridamole, trinitrine or isosorbide dinitrate or other drugs known for this purpose, such as the prostaglandins and drugs useful for treating sexual dysfunction;

[0086] a prostaglandin such as alprostadil (PGE1), prostacyclin (PGI2), dinoprost (prostaglandin F2-alpha) and misoprostol;

[0087] other drugs useful in treating male or female sexual dysfunction such as papaverine, dioxyline, ethaverine, minoxidil, nitroglycerin, alpha blockers, nitric oxide donors;

[0088] a corticosteroid such as betamethasone, betamethasone valerate, cortisone, dexamethasone, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, fluocinonide desonide, fluocinolone, fluocinolone acetonide, fluocortolone, halcinonide, halopredone, hydrocortisone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate methylprednisolone, prednisolone, prednisolone 21-phosphate, prednisone, triamcinolone, triamcinolone acetonide;

[0089] further examples of steroidal agents for use in the instant compositions include include cortodoxone, fluoracetonide, fludrocortisone, difluorsone diacetate, flurandrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and its other

esters, chloroprednisone, clorcortelone, descinolone, desonide, dichlorisone, difluprednate, flucloronide, flumethasone, flunisolide, flucortolone, fluoromethalone, fluperolone, fluprednisolone, meprednisone, methylmeprednisolone, paramethasone, cortisone acetate, hydrocortisone cyclopentylpropionate, cortodoxone, flucetonide, fludrocortisone acetate, flurandrenolone acetonide, medrysone, amcinafal, amcinafide, betamethasone, betamethasone benzoate, chloroprednisone acetate, clocortolone acetate, descinolone acetonide, desoximetasone, dichlorisone acetate, difluprednate, flucloronide, flumethasone pivalate, flunisolide acetate, fluperolone acetate, fluprednisolone valerate, paramethasone acetate, prednisolamate, prednival, triamcinolone hexacetonide, cortivazol, formocortal and nivazol;

[0090] an anti-hypertensive agent such as propanolol, prazosin, diltiazem or clonidine;

[0091] an insect repellent such as N,N-diethyl-meta-toluamide (DEET), ethyl butylacetylaminopropionate, oil of eucalyptus, or citronella;

[0092] an antiparkinsonian agent such as methyldopa or selegiline;

[0093] an antimigraine agent such as dihydroergotamine;

[0094] an antiulcer agent such as cimetidine;

[0095] an anticancer agent such as tamoxifen;

[0096] a nutritional supply such as vitamins, essential amino acids or essential fatty acids.

[0097] As mentioned above, the compositions of the invention may optionally contain active agents formed of a combination of several medicinal substances selected from the groups listed above.

Vehicles

[0098] The composition according to the invention may also comprise a solid,

semi-solid or liquid pharmaceutically acceptable vehicle, to help the active agent and skin penetration enhancer to be conveyed to the skin or other membrane, such as the nasal or oral mucosa, at an appropriate concentration and amount. The nature of the vehicle will depend upon the method chosen for topical administration of the composition.

[0099] The selection of a vehicle for this purpose presents a wide range of possibilities depending on the required product form of the composition.

[0100] It should be explained that vehicles are compositions which may include diluents, dispersants, or solvents for the active agent and penetration enhancer which therefore ensure that they can be applied to and distributed evenly over an appropriate area of the skin. Compositions according to this invention can include water as a vehicle, and/or at least one pharmaceutically acceptable vehicle other than water.

[0101] Vehicles other than water that can be used in compositions according to the invention can include solids or liquids such as emollients and moisturizers, solvents, humectants, thickeners, preservatives, colorants, fragrances, propellants and solid additives. Examples of types of such additives, which can be used singly or as mixtures, are as follows:

[0102] Emollients and moisturizers, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, ispropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polythylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate;

[0103] Propellants, such as trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethane, monochlorodifluoromethane, trichlorotrifluoroethane, propane, butane, isobutane, carbon dioxide;

[0104] Solvents, such as ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran. Preferably,

the solvent is selected for its ability to dissolve the active agent, and the SPE compound or SPE compounds, and one of ordinary skill in the art would understand which solvents would be suitable for such purposes, or how to determine which solvents would be appropriate;

[0105] Humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, gelatin;

[0106] Solid additives, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, tetra alkyl and/or trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymers, hydroxyalkylated cellulosics, sodium carboxymethyl cellulose.

[0107] The amount of the vehicle can comprise the balance of the composition, particularly where little or no other ingredients are present in the composition. Accordingly, the vehicle or vehicles can comprise from 0 to 99.99%, for example, from about 50 to about 99%, for example from about 70 to about 95%, for example from about 70 to about 99% by weight of the composition.

[0108] The above-described ingredients can be formulated with the skin penetration enhancer and active agent to form a composition suitable for topical application, including creams, lotions, ointments, gels, sprays, aerosols, and the like. In one embodiment, the active agent and skin penetration enhancer are dispersed within cream bases or ointment bases to form a cream or ointment.

[0109] Topical carriers may include conventional emulsifiers or other excipients including alginates, glyceryl stearate, PEG-100 stearate, cetyl alcohol, propylparaben, butylparaben, sorbitols, polyethoxylated sorbitan fatty esters (TWEENS), white soft paraffin (petrolatum), triethanolamine, aloe vera extract, lanolin, cocoa butter, and the like. Suitable topical carriers are well known to the skilled artisan.

Preparation and administration

[0110] The compositions according to the invention are well suited for transdermal administration and may be prepared, in a conventional manner, by mixing together the various constituents in the chosen proportions. Different active agents may yield different results with different skin penetration enhancers, solvent or carrier systems or other

ingredients in the formulation and in light of the present disclosure, the skilled artisan would be able to select an appropriate enhancer with the appropriate system for a given active agent.

[0111] The compositions of the invention thus obtained may be applied by any means to a predetermined area of skin, for example to an area of between 10 and 100 cm^2, for example 50 cm^2.

[0112] While the foregoing and following descriptions are given with respect to transdermal or percutaneous administration of drugs or other classes of active agent through human or animal skin, the principles and compositions disclosed herein are not so limited but will be generally applicable to administration of a broad spectrum of active agents, including medicines, drugs, pharmacologicals and non-bioactive (e.g., cosmetic) substances or agricultural chemicals for treating plants, and other viable animal membranes. In this regard, it will also be appreciated by those skilled in the art that certain substances may exert medicinal or pharmacological activity when used at high concentration while at lower concentration and/or for a lower extent of transmigration, e.g., without substantially reaching beyond the viable skin to the vascular or capillary network, will exert only a cosmetic effect or weaker pharmacological activity.

[0113] When the pharmaceutical compositions of this invention are in the form of a lotion, cream, emulsion, gel, solution, ointment or similar composition, the compositions may be spread as a film over the selected area of skin and, to this end, do not necessarily require intermediate propellant gases. Alternatively, the topical transdermal composition may also be incorporated into a transdermal delivery device, e.g., a patch.

[0114] In another embodiment of the present invention, the compositions may be administered by direct spraying using a doser pump of a type which is known and marketed for use without the aid of a propellant. If so desired, the compositions of the invention may, however, be administered by spraying from a container fitted with a dose valve, additionally containing a compressed propellant gas such as those mentioned above.

EXAMPLES

[0115] The following examples are given as particular embodiments of the invention and to demonstrate the practice and advantages thereof. It is understood that the examples are given by way of illustration and are not intended to limit the specification or the claims that follow in any manner.

Example 1

[0116] The following compositions were prepared as ethanolic solutions of the indicated active agents and skin penetration enhancing compounds, and subsequently tested for transdermal penetration.

TABLE 1

Sample #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Reagent:	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Ibuprofen									5	5	5	5	5	5	5	5									5	5									
Testosterone	1	1	1	1	1	1	1	1																			1								
PGE1																	1	1	1	1	1	1	1	1				2	2	2	2				
Hydroquinone																																3	3	3	3
t-Butyl Laurate	2	5	10						2	5	10						2	5	10											10					10
Lauryl Pivalate				2	5	10						2	5	10						2	5	10								10		10			
t-Butyl Decanoate																									10			10							
t-Butyl Myristate																										10	10		10						
SEPA 0009								10								10								10								10			
EtOH	97	94	89	97	94	89	99	89	93	90	85	93	90	85	95	85	97	94	89	97	94	89	99	89	85	85	89	88	88	88	88	87	87	97	87
Total	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

TABLE 1 Continued

Sample #	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57
Reagent	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Ibuprofen	5	5	5	5																		
Testosterone					1	1	1	1	1													
PGE1										1	1	1	1	1	2	2	2	2				
Buspirone HCl																			10	10	10	10
Lauryl Pivilate																				10		
t-Butyl Decanoate																					10	
Decel Pivalate	10				10					10					10							
Tetradecyl Pivalate		10				10					10					10						
N-Decyl Pivalamide			10				10		10			10		10			10					
N-Dodecyl Pivalamide				10				10					10					10				
SEPA																			10			
EtOH	85	85	85	85	89	89	89	89	89	89	89	89	89	89	88	88	88	88	68	68	68	76.5
Water																			12	12	12	13.5
Total of components	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Example 2

[0117] The following experiments were conducted to measure the flux of various active agents across human skin in the presence of an skin penetration enhancer. Human cadaver skin was obtained from AATB accredited tissue banks. The tissue was recovered within 15 hours of death or within 24 hours if the body was refrigerated, and prepared for these experiments using standard techniques.

[0118] Percutaneous absorption was measured using horizontal glass diffusion cells consisting of a donor and a receptor compartment (Franz-type diffusion cells, or static cells, supplied by Crown Glass Company of Somerville, NJ, U.S.A). The area available for diffusion was 0.635 cm^2 and the receptor compartment volume was 5.5 mL. The receptor chamber was filled, so the liquid interfaced with the skin membrane, with approximately 5 mL buffered saline and allowed to equilibrate to the correct temperature. Temperature of the skin surface was maintained at 32°C throughout the experiment by placing diffusion cells into dry block heater set on 37°C. The receptor compartment contents were continuously agitated by small PTFE-coated magnetic stirring bars .

[0119] Formulations were then applied using a micropipette. The pipette was weighed before and after application and the amounts applied were recorded. Following application of the products, the entire receptor phase was removed at regular time intervals using a syringe. Following the final receptor phase sample, the residual drug remaining on the surface of the skin was determined.

[0120] Analytical determinations were made by high performance liquid chromatography (HPLC) using an Agilent HPLC system equipped with a variable wavelength detector, column oven, in-line degasser and autosampler.

[0121] Data representing both the flux and cumulative transfer of active agent are reported graphically in the appended Figures. As can be seen from these Figures, the penetration of a variety of active agents through human skin may be enhanced using enhancers of formulas IA or IB, although not all enhancers are equally effective with all active agents. For example, the 2 pivalamides worked particularly well with PGE1, while lauryl pivalate and t-butyl decanoate were less effective with PGE1. On the other hand, the amide enhancers of the present invention work well with other hydrophobic active agents as seen, for example, in the PGE1 systems of Figures 9-10 and 13-14. Accordingly, it is understood that within the general guidelines provided herein and in view of the general level of skill in the art, the practitioner will be able to determine the

most appropriate combinations of the enhancer(s) of Formulas IA and/or IB for any particular active agent as well as any other ingredients, e.g., solvents and other additives as described herein.

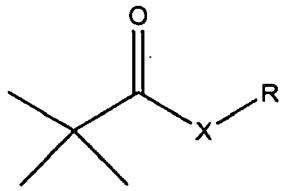
[0122] Having described specific embodiments of the present invention, it will be understood that many modifications thereof will readily appear or may be suggested to those skilled in the art, and it is intended therefore that this invention is limited only by the spirit and scope of the following claims.

What is claimed is:

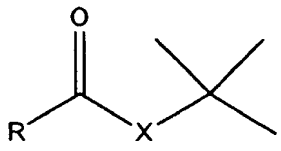
1. A pharmaceutical composition comprising:

a) at least one active agent; and

b) a skin penetration enhancer represented by the Formulas IA or IB



IA



IB

wherein:

R represents a linear, saturated or unsaturated, substituted or unsubstituted hydrocarbyl radical having at least 6 carbon atoms; and

X is either an oxygen atom or an NH radical.

2. The pharmaceutical composition according to claim 1, wherein the skin penetration enhancer comprises a compound of Formula IA.

3. The pharmaceutical composition according to claim 1, wherein the skin penetration enhancer comprises a compound of Formula IB.

4. The pharmaceutical composition according to claim 1 wherein R represents a linear C_6-C_{20} alkyl radical.

5. The pharmaceutical composition according to claim 1 wherein R represents a linear C_6-C_{16} alkyl radical.

6. The pharmaceutical composition according to claim 1 wherein R represents a linear C_6-C_{14} alkyl radical.

7. The pharmaceutical composition according to claim 1 wherein R represents a linear C_8-C_{14} alkyl radical.

8. The pharmaceutical composition according to claim 1 wherein R represents an octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, or tetradecyl radical.

9. The pharmaceutical composition according to any one of claims 1-8 wherein R represents an octyl, decyl, dodecyl or tetradecyl radical.

10. The pharmaceutical composition according to any one of claims 1-8 wherein X represents an oxygen atom.

11. The pharmaceutical composition according to any one of claim 1-8 wherein X represents an N-H radical.

12. The pharmaceutical composition according to claim 1 wherein said skin penetration enhancer is decyl pivalate, dodecyl pivalate, tetradecyl pivalate, N-decyl pivalamide, N-dodecyl pivalamide, tert-butyl decanoate, tert-butyl laurate or tert-butyl myristate.

13. The pharmaceutical composition according to any one of claims 1-12 further comprising a pharmaceutically acceptable vehicle.

14. The pharmaceutical composition of claim 13 wherein said vehicle is a liquid.

15. The pharmaceutical composition of claim 13 wherein said vehicle is a cream.

16. The pharmaceutical composition of claim 13 wherein said vehicle is a lotion.

17. The pharmaceutical composition of claim 13 wherein said vehicle is an ointment.

18. The pharmaceutical composition of claim 13 wherein said vehicle is a gel.

19. The pharmaceutical composition of claim 13 wherein said vehicle is a spray.

20. The pharmaceutical composition of claim 13 wherein said vehicle is an aerosol.

21. The pharmaceutical composition of claim 1 wherein said active agent comprises at least one compound of amorolfine, isoconazole, clotrimazole, econazole, miconazole, nystatin, terbinafine, bifonazole, amphotericin, griseofulvin, ketoconazole, fluconazole and flucytosine, salicylic acid, fezatione, ticlatone, tolnaftate, triacetin or zinc pyrithione.

22. The pharmaceutical composition of claim 1 wherein said active agent comprises at least one compound of papaverine, dioxyline, ethaverine, minoxidil or nitroglycerin.

23. The pharmaceutical composition of claim 1 wherein said active agent comprises at least one compound of alprostadil (PGE1), prostacyclin (PGI2), dinoprost (prostaglandin F2-alpha) or misoprostol.

24. The pharmaceutical composition of claim 1 wherein said active agent comprises at least one compound of tolmetin, diclofenac, ketorolac, ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin, mefenamic acid, meclofenamic acid, fhilenamic acid, piroxicam, tenoxicam, phenylbutazone, oxyphenthatrazone or nabumetone.

25. The pharmaceutical composition according to claim 1 wherein said active agent is buspirone hydrochloride.

26. The pharmaceutical composition according to claim 1 wherein said active agent is ibuprofen and said skin penetration enhancer is lauryl pivalate.

27. The pharmaceutical composition according to claim 1 wherein said active agent is ibuprofen and said skin penetration enhancer is t-butyl decanoate.

28. The pharmaceutical composition according to claim 1 wherein said active agent is testosterone and said skin penetration enhancer is lauryl pivalate.

29. The pharmaceutical composition according to claim 1 wherein said active agent is testosterone and said skin penetration enhancer is t-butyl myristate.

30. The pharmaceutical composition according to claim 1 wherein said active agent is testosterone and said skin penetration enhancer is t-butyl decanoate .

31. The pharmaceutical composition according to claim 1 wherein said active agent is PGE1 and said skin penetration enhancer is t-butyl laurate.

32. The pharmaceutical composition according to claim 1 wherein said active agent is PGE1 and said skin penetration enhancer is tetradecyl pivalate.

33. The pharmaceutical composition according to claim 1 wherein said active agent is PGE1 and said skin penetration enhancer is n-decyl pivalamide.

34. The pharmaceutical composition according to claim 1 wherein said active agent is PGE1 and said skin penetration enhancer is n-dodecyl pivalamide.

35. The pharmaceutical composition according to claim 1 wherein said active agent is hydroquinone.

Figure 1

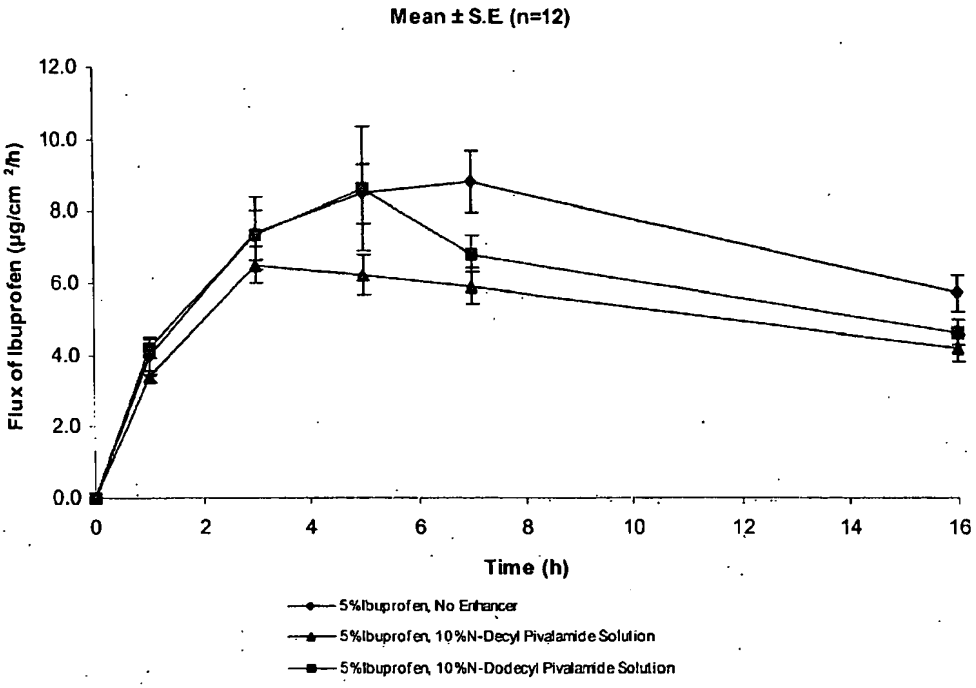

Mean ± S.E. (n=12)
Flux of Ibuprofen (µg/cm ²/h)
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0
2
4
6
8
10
12
14
16
Time (h)
5%Ibuprofen, No Enhancer
5%Ibuprofen, 10%N-Decyl Pivalamide Solution
5%Ibuprofen, 10%N-Dodecyl Pivalamide Solution

Figure 2

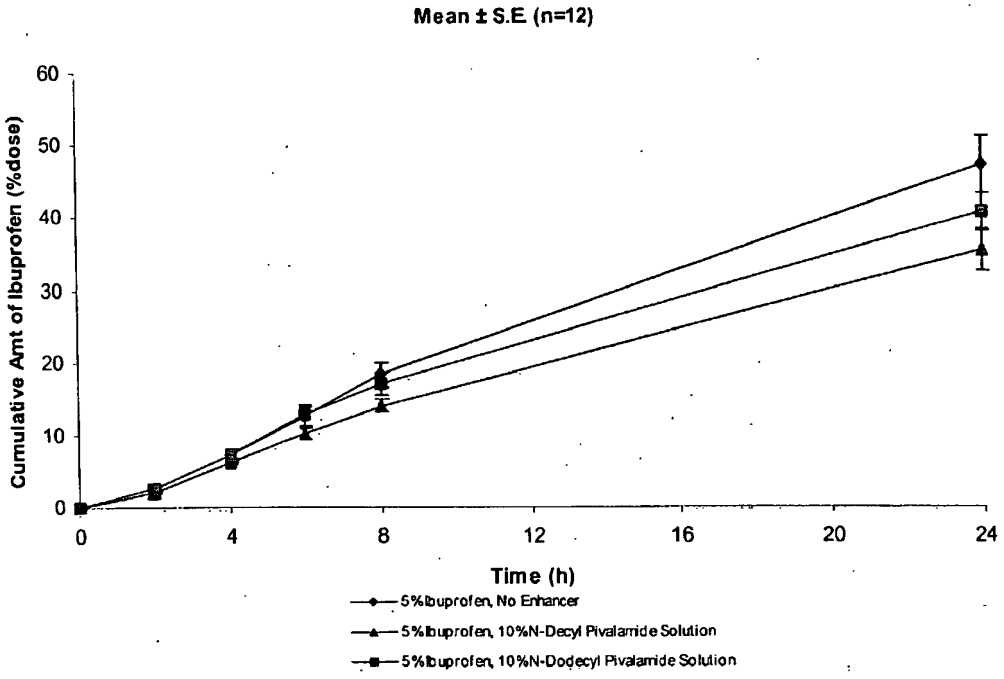

Mean ± S.E. (n=12)
Cumulative Amt of Ibuprofen (%dose)
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Time (h)
5%Ibuprofen, No Enhancer
5%Ibuprofen, 10%N-Decyl Pivalamide Solution
5%Ibuprofen, 10%N-Dodecyl Pivalamide Solution

Figure 3

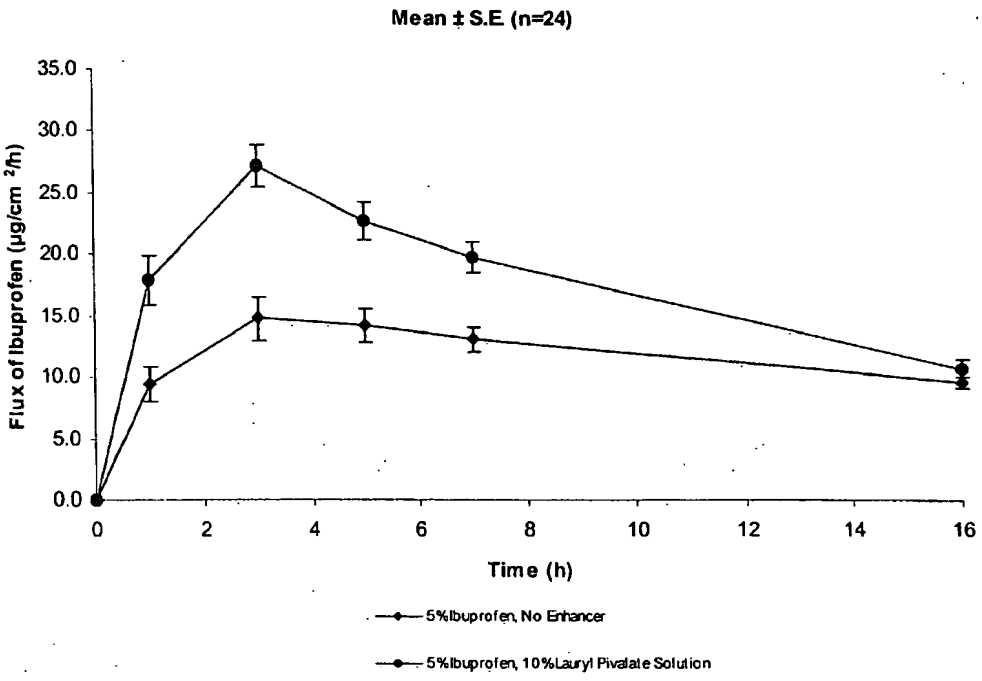

Mean ± S.E. (n=24)
Flux of Ibuprofen (µg/cm ²/h)
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
0
2
4
6
8
10
12
14
16
Time (h)
5%Ibuprofen, No Enhancer
5%Ibuprofen, 10%Lauryl Pivalate Solution

Figure 4

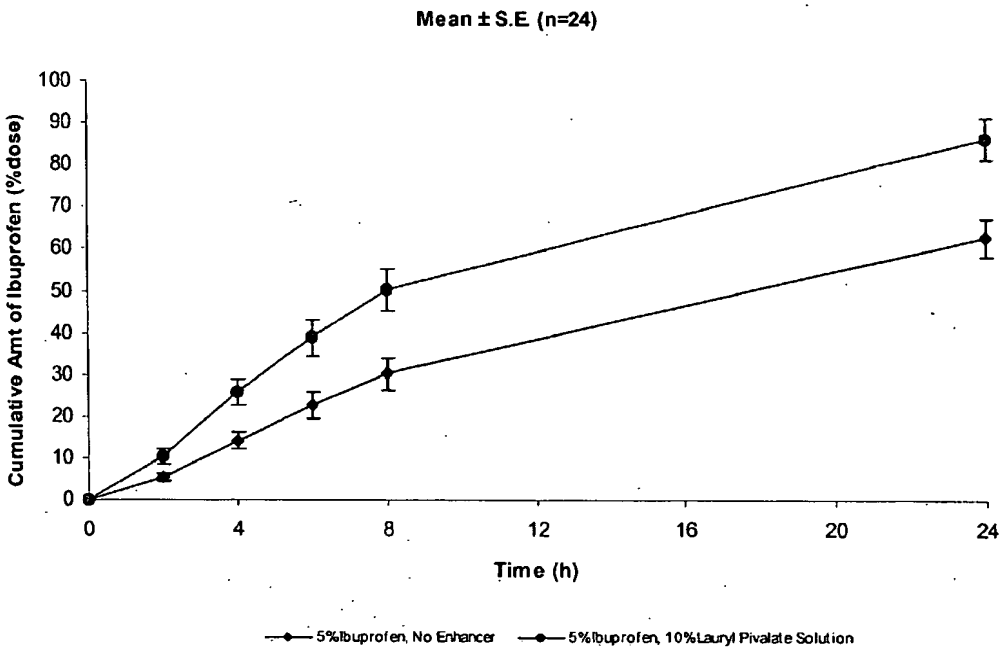

Mean ± S.E. (n=24)
Cumulative Amt of Ibuprofen (%dose)
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Time (h)
5%Ibuprofen, No Enhancer
5%Ibuprofen, 10%Lauryl Pivalate Solution

Figure 5

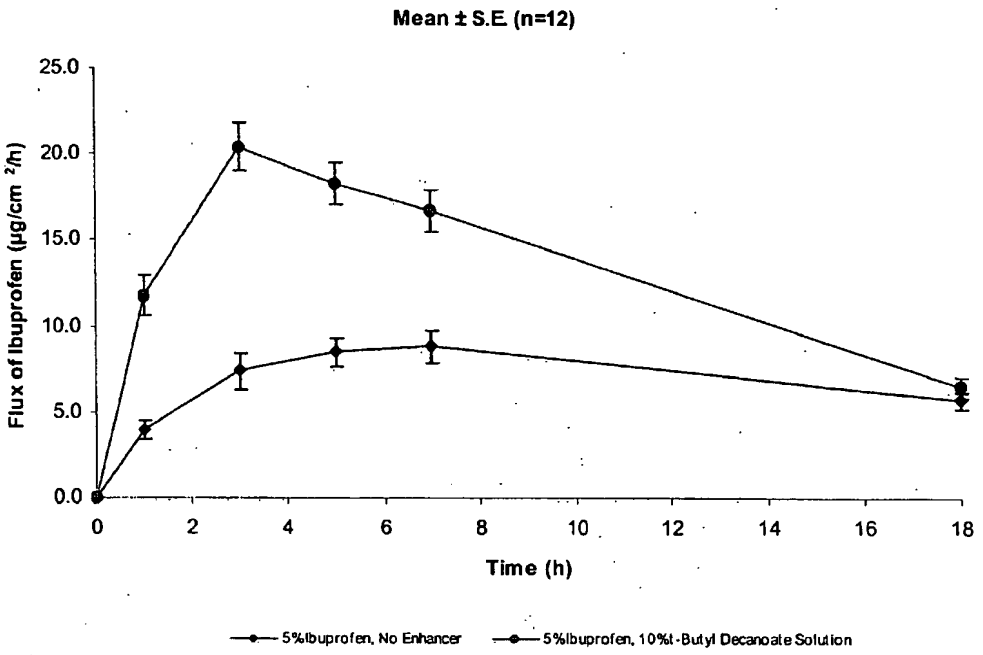

Mean ± S.E. (n=12)
Flux of Ibuprofen (µg/cm ²/h)
25.0
20.0
15.0
10.0
5.0
0.0
0
2
4
6
8
10
12
14
16
18
Time (h)
5%Ibuprofen, No Enhancer
5%Ibuprofen, 10%t-Butyl Decanoate Solution

Figure 6

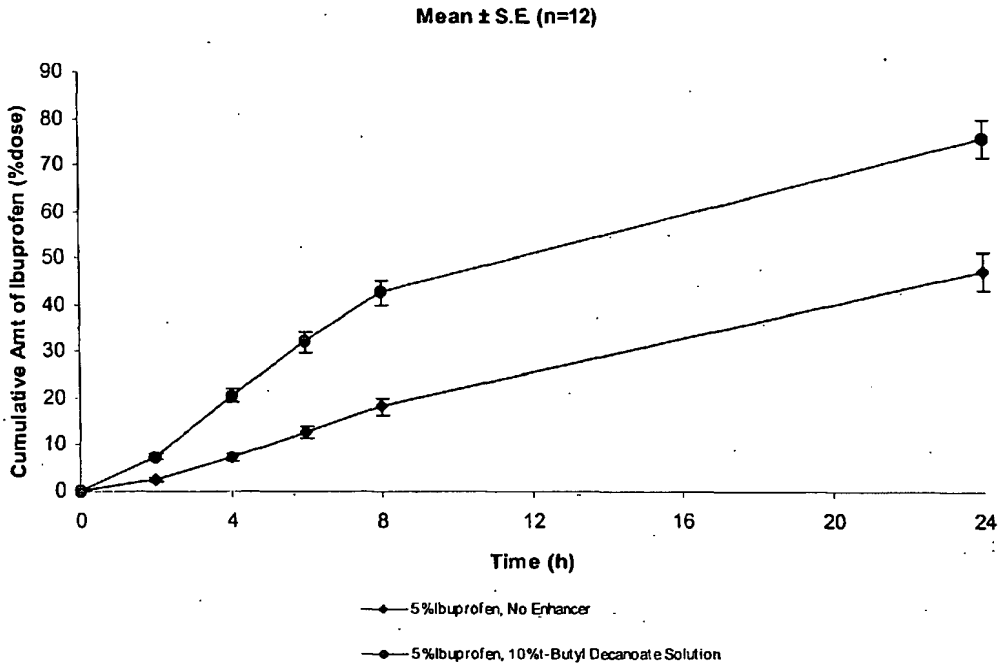

Mean ± S.E. (n=12)
Cumulative Amt of Ibuprofen (%dose)
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Time (h)
5%Ibuprofen, No Enhancer
5%Ibuprofen, 10%t-Butyl Decanoate Solution

Figure 7

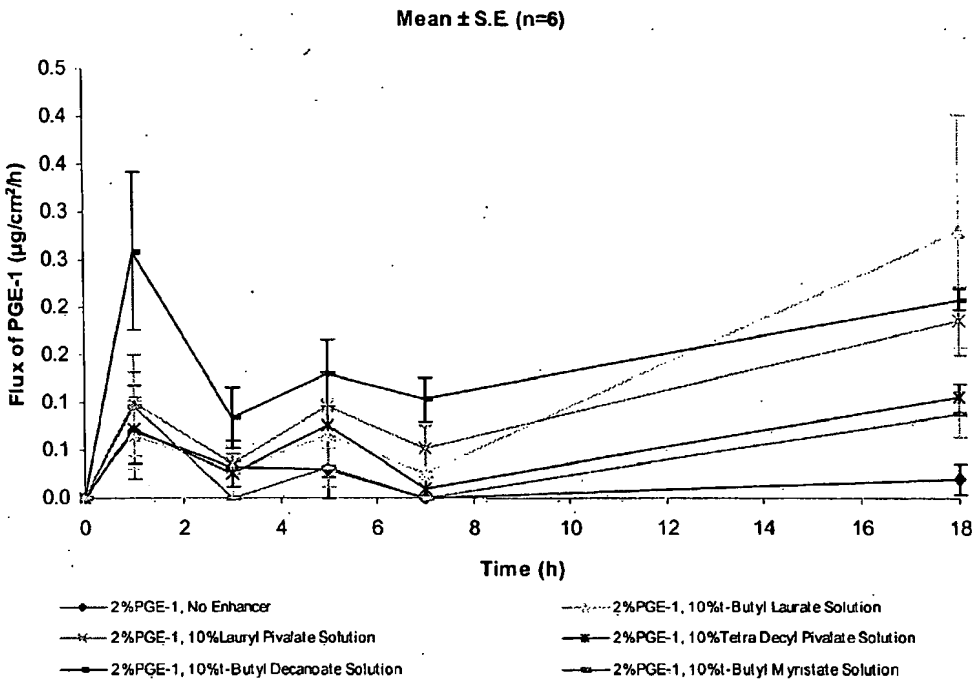

Mean ± S.E. (n=6)
Flux of PGE-1 (µg/cm²/h)
0.5
0.4
0.4
0.3
0.3
0.2
0.2
0.1
0.1
0.0
0
2
4
6
8
10
12
14
16
18
Time (h)
2%PGE-1, No Enhancer
2%PGE-1, 10%t-Butyl Laurate Solution
2%PGE-1, 10%Lauryl Pivalate Solution
2%PGE-1, 10%Tetra Decyl Pivalate Solution
2%PGE-1, 10%t-Butyl Decanoate Solution
2%PGE-1, 10%t-Butyl Myristate Solution

Figure 8

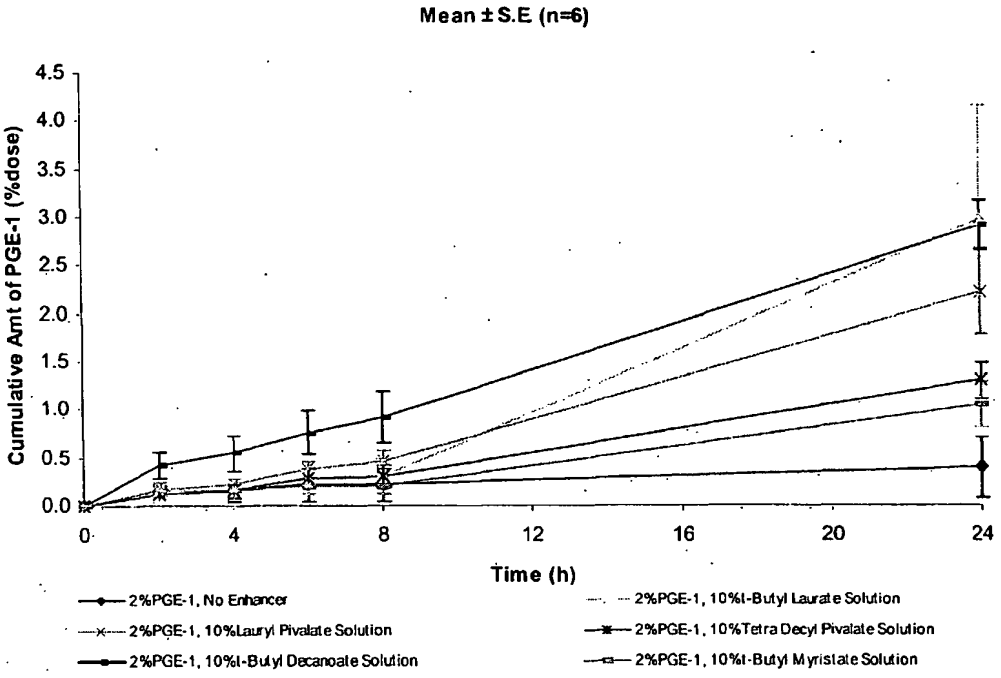

Mean ± S.E (n=6)
Cumulative Amt of PGE-1 (%dose)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
4
8
12
16
20
24
Time (h)
2%PGE-1, No Enhancer
2%PGE-1, 10%I-Butyl Laurate Solution
2%PGE-1, 10%Lauryl Pivalate Solution
2%PGE-1, 10%Tetra Decyl Pivalate Solution
2%PGE-1, 10%I-Butyl Decanoate Solution
2%PGE-1, 10%I-Butyl Myristate Solution

Figure 9

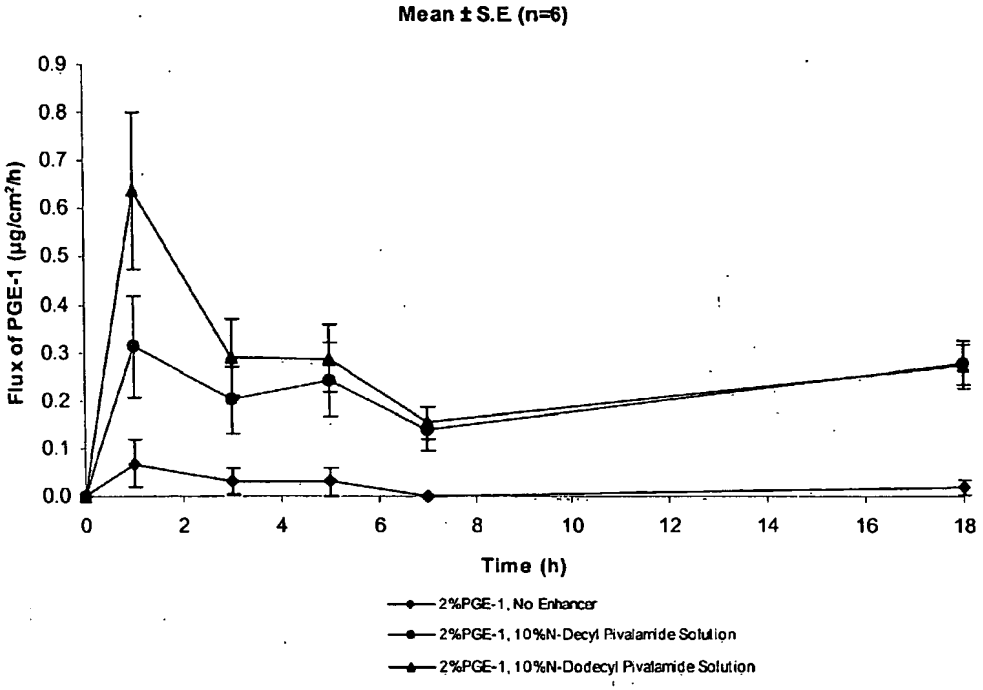

Mean ± S.E. (n=6)
Flux of PGE-1 (µg/cm²/h)
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
12
14
16
18
Time (h)
2%PGE-1, No Enhancer
2%PGE-1, 10%N-Decyl Pivalamide Solution
2%PGE-1, 10%N-Dodecyl Pivalamide Solution

Figure 10

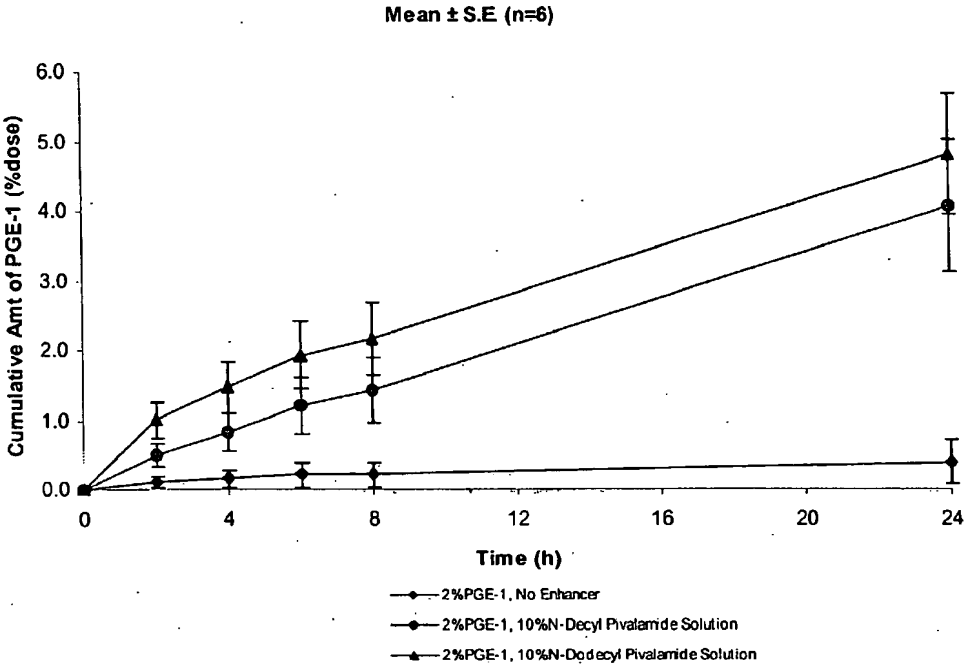

Mean ± S.E (n=6)
Cumulative Amt of PGE-1 (%dose)
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0
4
8
12
16
20
24
Time (h)
2%PGE-1, No Enhancer
2%PGE-1, 10%N-Decyl Pivalamide Solution
2%PGE-1, 10%N-Dodecyl Pivalamide Solution

Figure 11

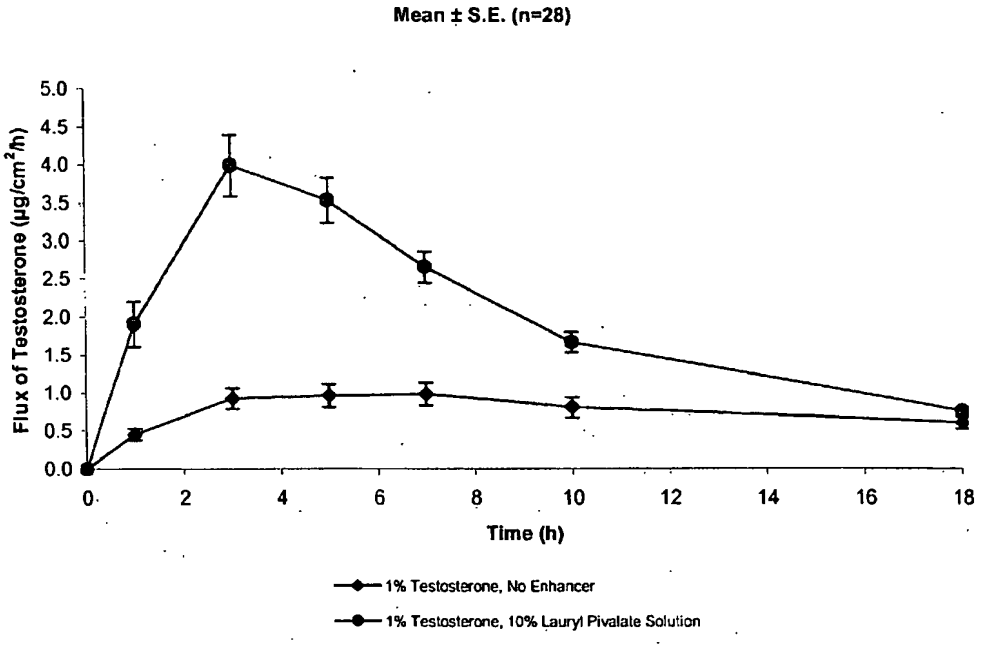

Mean ± S.E. (n=28)
Flux of Testosterone (µg/cm²/h)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
2
4
6
8
10
12
14
16
18
Time (h)
1% Testosterone, No Enhancer
1% Testosterone, 10% Lauryl Pivalate Solution

Figure 12

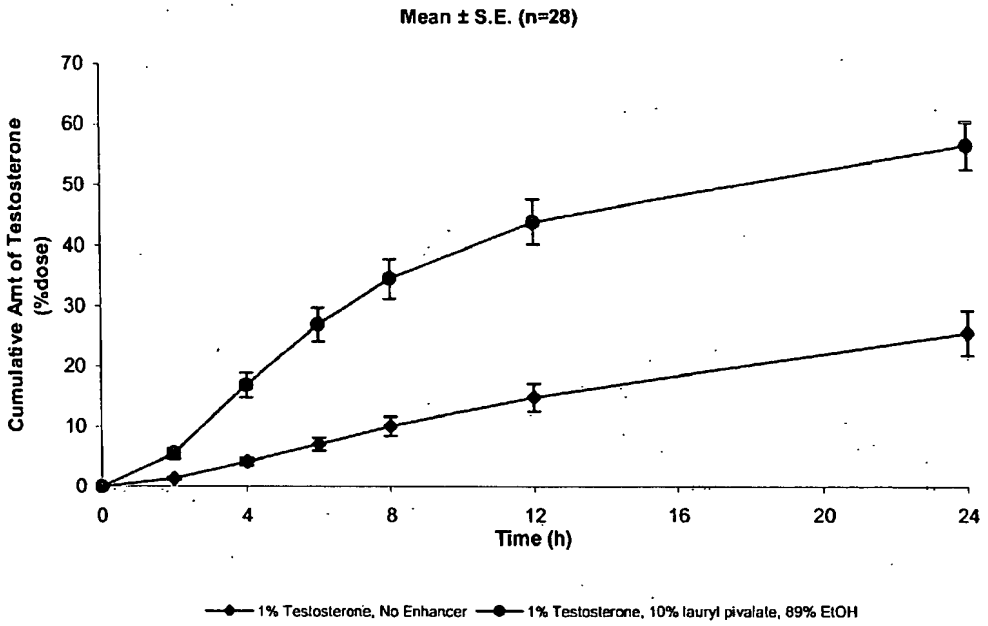

Mean ± S.E. (n=28)
Cumulative Amt of Testosterone (%dose)
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Time (h)
1% Testosterone, No Enhancer
1% Testosterone, 10% lauryl pivalate, 89% EtOH

Figure 13

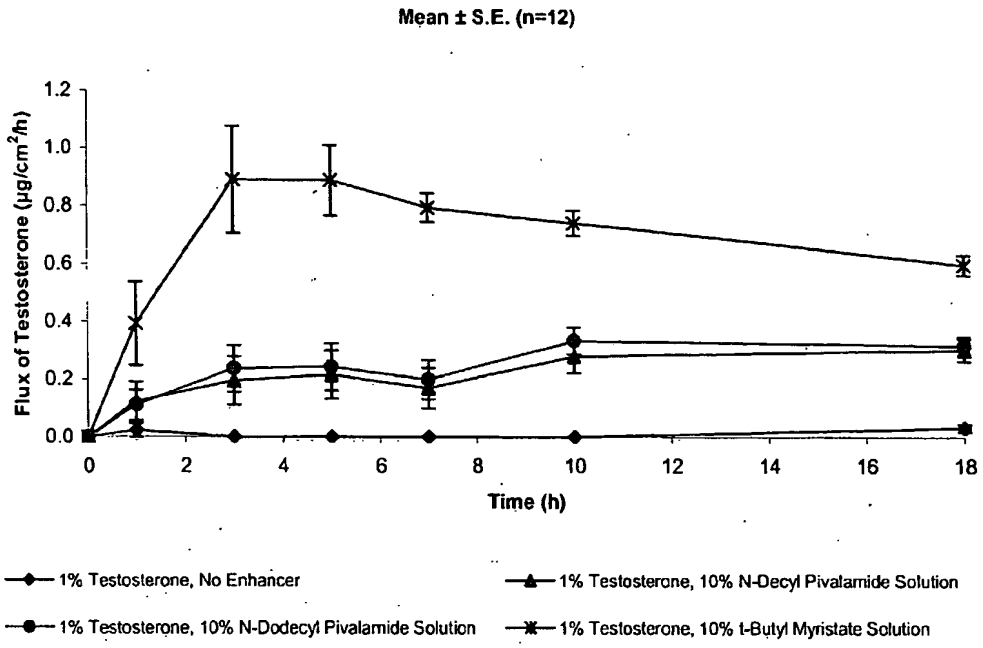

Mean ± S.E. (n=12)
Flux of Testosterone (µg/cm²/h)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
16
18
Time (h)
1% Testosterone, No Enhancer
1% Testosterone, 10% N-Decyl Pivalamide Solution
1% Testosterone, 10% N-Dodecyl Pivalamide Solution
1% Testosterone, 10% t-Butyl Myristate Solution

Figure 14

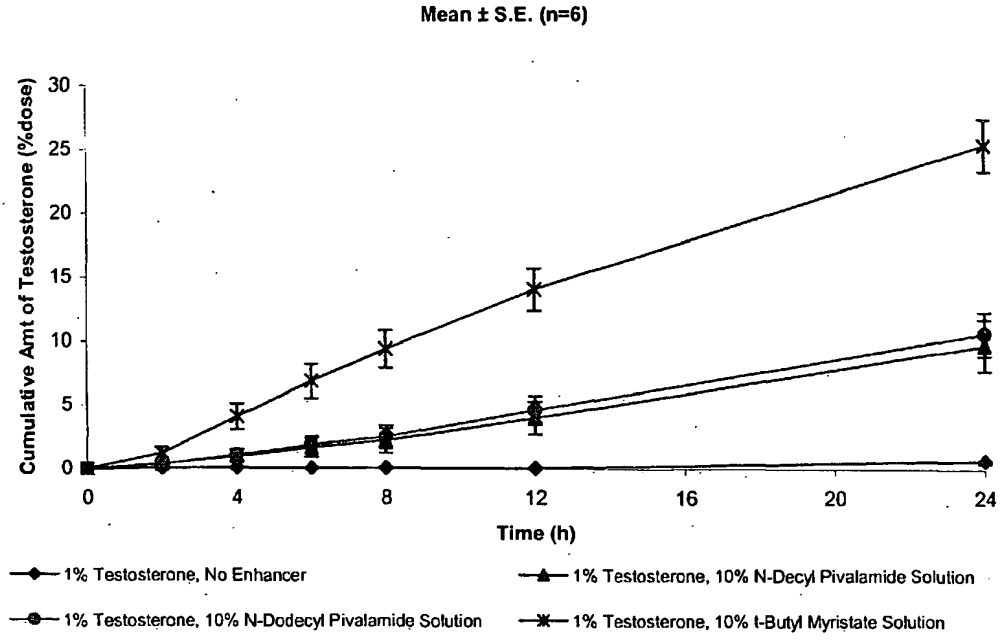

Mean ± S.E. (n=6)
Cumulative Amt of Testosterone (%dose)
30
25
20
15
10
5
0
0
4
8
12
16
20
24
Time (h)
1% Testosterone, No Enhancer
1% Testosterone, 10% N-Decyl Pivalamide Solution
1% Testosterone, 10% N-Dodecyl Pivalamide Solution
1% Testosterone, 10% t-Butyl Myristate Solution

Figure 15

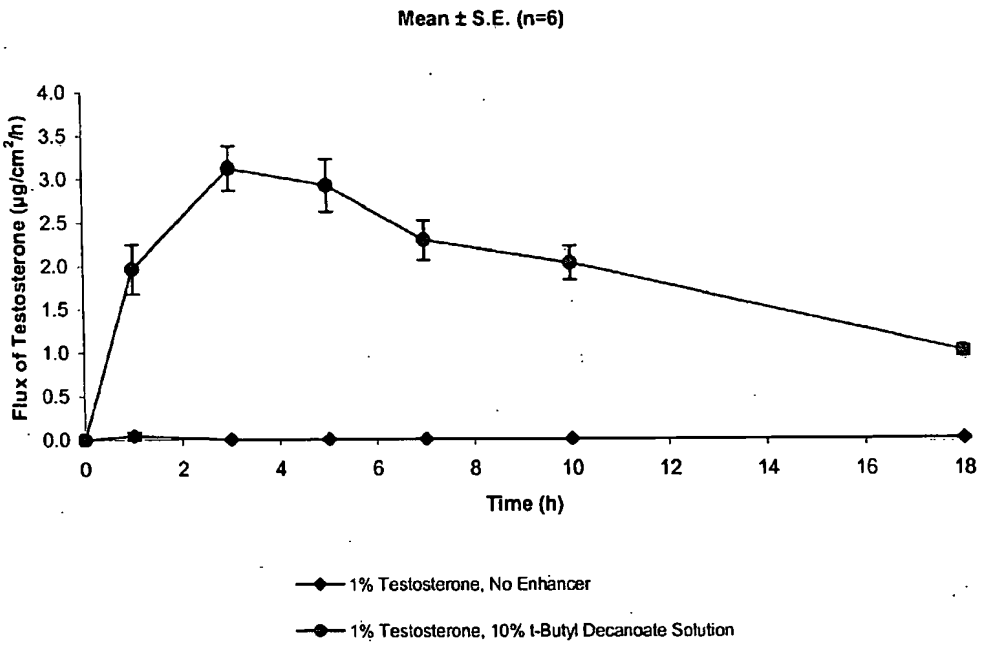
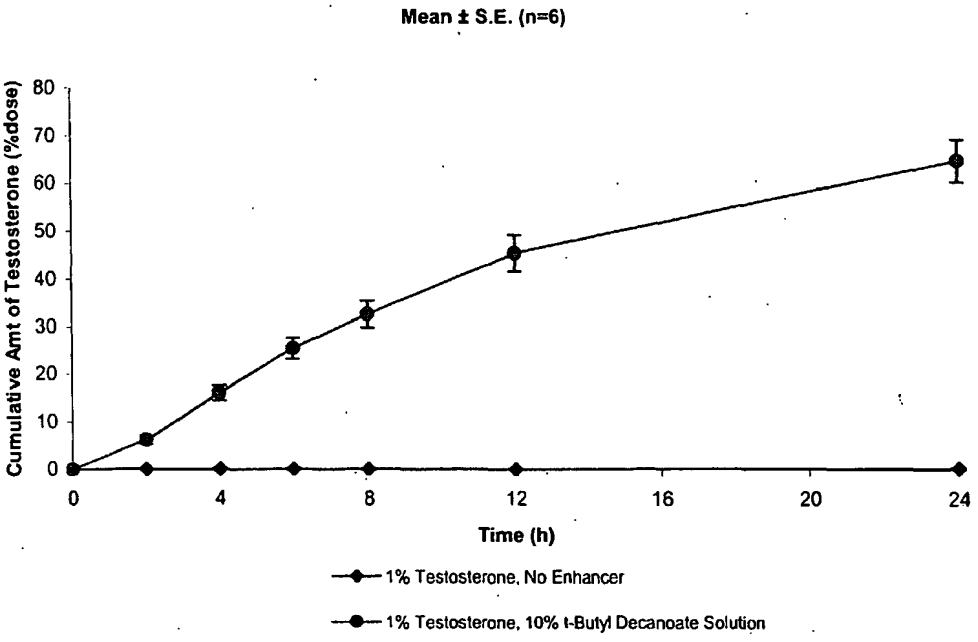

Mean ± S.E. (n=6)
Flux of Testosterone (µg/cm²/h)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
2
4
6
8
10
12
14
16
18
Time (h)
1% Testosterone, No Enhancer
1% Testosterone, 10% t-Butyl Decanoate Solution

Figure 16


Mean ± S.E. (n=6)
Cumulative Amt of Testosterone (%dose)
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Time (h)
1% Testosterone, No Enhancer
1% Testosterone, 10% t-Butyl Decanoate Solution